IN THE DRAWINGS

In the present Amendment and Response to the Office Action of January 24, 2007, SED ID Nos. 44 and 45 have been added to Figure 20A, and SEQ ID Nos. 46 and 47 have been added to Figure 20B. Please see the labeled Replacement Sheets that are attached to this document.

REMARKS

I. STATUS OF THE APPLICATION

Claims 1 – 28 were filed in the original application. In the Amendment and Response to Restriction Requirement mailed May 1, 2006, claims 1 – 12, 14, 21, and 26 – 28 were cancelled, claims 13, 16 – 19, and 22 – 23 were amended, and claims 29 – 45 were added. In the Response to Office Action mailed August 3, 2006 claim 29 was cancelled, and claims 13, 16, 18, 19, 22, 30, 31, 34, were amended. In the present Amendment and Response to the Office Action mailed January 24, 2007 claims 13, 15 – 20, 22 – 25, and 30 – 45 are cancelled, and claims 46 – 90 are added. Support for the added claims is found throughout the Specification, and is discussed below at Section III.B. Therefore, claims 46 – 90 are currently pending.

In the Office Action there are 4 rejections to the claims, one informality and one objection to the Drawings. The currently pending rejections, objection and informality are:

1. Claim 39 recites "said standard segment". The Examiner notes "It would have been 'said segment'."

2. Claims 39 – 40 are rejected under 35 U.S.C. 112, second paragraph as allegedly being indefinite.

3. Claims 34 – 37, 39 – 40, and 43 – 44 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Torroni et al. (Genetics, Vol. 144, page 1835-1850, 1996) (hereinafter "Torroni").

4. Claims 13, 15 – 17, 19 – 20, 22 – 25, 30 – 33, 41 – 42 and 45 are rejected under 35 U.S.C. 103(a) as allegeldly being unpatentable over Torroni in

view of Aaserud et al. (Am Soc Mass Spectrometry, Vol. 7, page 1266 – 1269, 1996 (hereinafter "Aaserud").

5. Claims 18 and 38 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Torroni in view of Aaserud and further in view of Oefner et al (US 6,453,244) (hereinafter "Oefner").

6. The Examiner notes: "The amendment did not incorporate SEQ ID No. in the Fig 20A and 20B, which represent sequences with more than 10 bases. Thus the objection to the drawings is maintained herein."

II. STATUS OF THE INFORMALITY

In the Office Action of January 24, 2007 the Examiner comments:

"(i) claim 39 recites "said standard segment". "It would have been 'said segment'." (Office Action of January 24, 2007, page 2.)

The Applicants note that in the present Amendment and Response to Office of January 24, 2007, Claim 39 has been cancelled thereby rendering the Examiner's comment moot.

III. STATUS OF THE REJECTIONS

A. Rejection under 35 USC §112

In the Office Action of January 24, 2007 the Examiner notes:

"Claim 39 recites the limitation "said standard segment" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim because the

independent claim 34, upon which the instant claim depends recite "a segment" and thus the limitation in the instant claims "said standard segment' lacks support." (Office Action of January 24, 2007, page 2.)

The Applicants note that in the present Amendment and Response to Office of January 24, 2007, Claim 39 has been cancelled thereby rendering the Examiner's comment moot.

As well, newly added claim 54 reads:

"54. (new) The forensic method of claim 46, wherein said one or more segments of mitochondrial DNA comprises a portion of a hypervariable region of mitochondrial DNA."

And, newly added claim 73 reads:

"73. (new) The forensic method of claim 65, wherein said one or more segments of mitochondrial DNA comprises a portion of a hypervariable region of mitochondrial DNA."

The Applicants note that newly added claims 54 and 73 add no new subject matter.

In view of the above, the Applicants respectfully request that this rejection be withdrawn.

B. Rejection under 35 USC §102(b)

In the Office Action of January 24, 2007, claims 34 – 37, 39 – 40, and 43 – 44 are rejected as allegedly being anticipated by Torroni. (Office Action of January 24, 2007, page 3.)

The Federal Circuit has stated the relevant analysis for anticipation as follows:

"A claim is anticipated only if each and every element as set forth in the claims is found, either expressly or inherently described, in a single prior art reference."[1]

The Applicants respectfully disagree with the rejection. However, in order to expedite the patent application process in a manner consistent with the U.S. Patent and Trademark Office's Patent Business Goals (PBG)[2], and without waiving the right to prosecute the amended or cancelled claims (or similar claims) in the future, in the present Amendment and Response to Office Action of January 24, 2007, newly added claim 65 (formerly claim 34) reads:

"65. A forensic method of mitochondrial DNA analysis comprising the steps of:

providing a forensic evidence sample;

amplifying one or more segments of mitochondrial DNA obtained from said forensic evidence sample to obtain one or more amplification products;

determining the molecular masses of said one or more amplification products by mass spectrometry, without sequencing said one or more amplification products;

calculating base compositions of said one or more amplification products from said molecular masses; and

comparing said base compositions of said one or more amplification products with at least one database comprising a plurality of known molecular masses from said one or more segments of mitochondrial DNA from a plurality of subjects, thereby reaching a forensic conclusion.

The Applicants respectfully submit that Torroni fails to teach each and every element as set forth in the claims. For example, Torroni does not teach or suggest a forensic evidence sample (claim 65, formerly claim 34). Support for a forensic evidence

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[1] *Verdegaal Bros. V. Union Oil of California*, 2 USPQ2d 1051, 1053 (Fed.Cir. 1987).
[2] 65 Fed. Reb. 54603 (Sept. 8, 2000).

sample may be found throughout the Specification at, for example, paragraph 0009 ("Mitochondrial DNA analysis will continue to be a powerful tool for law enforcement officials in the years to come as other applications are developed, validated, and applied to forensic evidence." and "More and more individuals are learning about the value of mtDNA sequencing for obtaining useful information from evidentiary samples that are small, degraded, or both."), and paragraph 0098 ("In other embodiments of the invention, the methods disclosed herein can be used for forensics. As used herein, "forensics" is the study of evidence discovered at a crime or accident scene and used in a court of law. "Forensic science" is any science used for the purposes of the law, in particular the criminal justice system, and therefore provides impartial scientific evidence for use in the courts of law, and in a criminal investigation and trial.").

As well, Torroni does not teach or suggest determining molecular masses by mass spectrometry (claim 65). Support for mass spectrometry may be found throughout the Specification at, for example, paragraph 0076 ("Mass spectrometry (MS)-based detection of PCR products provides a means for determination of BCS which has several advantages. MS is intrinsically a parallel detection scheme without the need for radioactive or fluorescent labels, since every amplification product is identified by its molecular mass. The current state of the art in mass spectrometry is such that less than femtomole quantities of material can be readily analyzed to afford information about the molecular contents of the sample.") Nor does Torroni teach or suggest calculating base compositions of mitochondrial DNA amplification products from molecular masses determined by mass spectrometry.

Clearly, Torroni is missing not just one but multiple elements of the claims set forth in the present application. Accordingly, Torroni does not teach or suggest the forensic methods of mitochondrial DNA analysis of the present application.

In view of the above, the Applicants request that this rejection be withdrawn.

C. Rejection under 35 USC §103(a)

A *prima facie* case of obviousness requires the Examiner to cite to a reference which a) discloses all the elements of the claimed invention, b) suggests or motivates one of ordinary skill in the art to combine the claim elements to yield the claimed invention, and c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of these three requirements negates a finding of a *prima facie* case and, without more, entitles the Applicants to allowance of the claims in issue. (MPEP)

1. Torroni in View of Aaserud

a. Missing elements in the Examiner's Combination of Torroni and Aaserud

In the Office Action of January 24, 2007 the Examiner argues:

> "It would have been prima facie obvious to a person of ordinary skill in the art at the time was made to modify the method of mtDNA analysis taught by Torroni et al in a manner as taught by Aaserud et al. by incorporating measuring base-composition by mass spectrometry for the purpose of enhancing sensitivity of the method for analyzing sequence variations in said target nucleic acids." (Office Action of January 24, 2007, page 6).

The Applicants respectfully disagree. Torroni in view of Aaserud does not teach or suggest the limitation "providing a forensic evidence sample" (claim 46, formerly claim 13).

As well, Torroni in view of Aaserud does not teach or suggest "a method of characterizing heteroplasmy of a segment of mitochondrial DNA of an individual" (claim 84, formerly claim 22). In the Office Action of January 24, 2007 the Examiner never specifically addresses independent claim 22 drawn to characterizing heteroplasmy in mitochondrial DNA, other than list claim 22 in the Examiner's catalog of rejected claims. In the Office Action of January 24, 2007 the Examiner's only consideration of claims

drawn to characterizing heteroplasmy appears with regard to dependent claim 45. The Examiner argues:

> "Torroni et al. also teach . . . with regard to claim 45, length or single nucleotide polymorphism heteroplasmy (see page 1836, col 2, line 1-14, page 1839, table 3)." (Office Action of January 24, 2007, page 5).

The Applicants respectfully disagree. Contrary to the Examiner's arguments, Torroni in view of Aaserud does not teach or suggest a method of characterizing heteroplasmy of a segment of mitochondrial DNA of an individual. Torroni describes detection of single nucleotide variations that are polymorphic within and between members of particular populations *i.e.*, Finns, Swedes or Tuscans. Torroni does not teach or suggest characterizing heteroplasmy of mitochondrial DNA in a sample from a single subject of the presently claimed invention. This distinction is clearly apparent at paragraph 0010 of the Specification:

> "Another complicating factor in the forensic analysis of mtDNA is the occurrence of heteroplasmy wherein the pool of mtDNAs in a given cell is heterogeneous due to mutations in individual mtDNAs. There are two forms of heteroplasmy found in mtDNA. Sequence heteroplasmy (also known as point heteroplasmy) is the occurrence of more than one base at a particular position or positions in the mtDNA sequence. Length heteroplasmy is the occurrence of more than one length of a stretch of the same base in a mtDNA sequence as a result of insertion of nucleotide residues. Heteroplasmy is a problem for forensic investigators since a sample from a crime scene can differ from a sample from a suspect by one base pair and this difference may be interpreted as sufficient evidence to eliminate that individual as the suspect. Hair samples from a single individual can contain heteroplasmic mutations at vastly different concentrations and even the root and shaft of a single hair can differ." (Specification, paragraph 0010.)

As well, the Examiner's combination of Torroni in view of Aaserud fails to teach or suggest numerous additional elements of the presently claimed invention, for example: comparing molecular masses of restriction fragments with at least one database comprising a plurality of known molecular masses from one or more segments of mitochondrial DNA from a plurality of subjects, thereby reaching a forensic conclusion (claim 50); animal subjects (claims 51 and 70); one amplification product that is generated from two hypervariable portions of the noncoding region of mitochondrial DNA using flanking primers (claims 56 and 75); segments of mitochondrial DNA that comprise the entire mitochondrial DNA of a subject (claims 57 and 76); a Federal Bureau of Investigation mitochondrial DNA database (claims 64 and 83); comparing base compositions of restriction fragments with at least one database comprising a plurality of known base compositions from one or more segments of mitochondrial DNA from a plurality of subjects, thereby reaching a forensic conclusion (claim 69); characterization of a rate of naturally occurring mutations in mitochondrial DNA in an individual (claim 86); mitochondrial diseases (claims 87 and 88); characterizing heteroplasmy of a segment of mitochondrial DNA of a subject wherein a sample from the subject is a forensic evidence sample (claim 90); and determining the relative amounts of said one or more amplification products from the abundance of mass spectral peaks corresponding to said one or more amplification products (claims 61 and 80).

Clearly, the Examiner's combination of Torroni in view of Aaserud is missing not just one but multiple elements of the claims set forth in the present application. Accordingly, Torroni in view of Aaserud does not teach or suggest the forensic methods of DNA analysis of the presently claimed invention.

In view of the above, the Applicants request that this rejection be withdrawn.

b. The Examiner Provides no Motivation to Combine Torroni and Aaserud

In the Office Action of January 24, 2007 the Examiner argues:

"One skilled in the art would have been motivated to combine the method of analyzing mtDNA as taught by Torroni et al. with a step determining base composition measurement by using mass spectrometry as taught by Aaserud et al. because the ordinary artisan would have a reasonable expectation of success that inclusion of said limitation would result in a sensitive comparison of base composition variations in mtDNA and accurate measurement of base compositions in said target because Aaserud et al explicitly taught that the mass spectrometry measures accurate molecular masses thereby providing correct base compositions of a target nucleic acid (see abstract on page 1266) and such modification is considered as obvious over cited prior art." (Office Action of January 24, 2007, page 6). (Emphasis added.)

The Applicants respectfully disagree. Alone or in combination, Torroni and Aaserud fail to teach, suggest or motivate the ordinary artisan to make the Examiner's combination of references. The Examiner does not, and cannot, point to which specific teachings in the cited references motivate the ordinary artisan to combine the claimed elements thereby arriving at the forensic method of mitochondrial DNA analysis of the present application. Nor has the Examiner provided any other evidence that teaches or suggests the Examiner's combination. The Examiner's requirement to provide evidence of the motivation to combine the Examiner's references is absolute.[3] In the Final Office Action of January 24, 2007 the Examiner has provided no supporting objective evidence sustaining the Examiner's conjecture with regard to what an ordinary artisan would or would not have been motivated to do.

Torroni describes haplotypes and haplogroups as tools for molecular anthropology and human evolutionary studies in populations. Torroni does not teach, suggest or even mention forensic methods or forensic applications. As well, Torroni does not teach, suggest or even mention mass spectrometry, molecular mass analysis, base compositions, or mitochondrial DNA heteroplasmy. Aaserud describes base composition

[3] *In re Kotzab*, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000).

analysis by mass spectrometry using synthetic 64-mer single stranded DNA monomers (see, for example, footnote 17, page 1269, column 2). Aaserud does not teach, suggest or even mention forensic methods or forensic applications. As well, Aaserud does not teach, suggest or even mention mitochondrial DNA or mitochondrial DNA heteroplasmy.

Merely because the Examiner's references could be combined or modified does not render the resultant combination obvious unless the prior art suggests the combination.[4,5] The Applicants submit that the Examiner's references cannot be considered collectively until the Examiner points to evidence of a motivation to combine the Examiner's cited references. The purpose behind this obligation is to prevent the Examiner, as here, from using the invention itself together with hindsight reconstruction to defeat the patentability of the invention. Moreover, the law does not regard the Examiner as one skilled in the art. ("[T]he examiner's assumptions do not constitute the disclosure of the prior art."[6] "[W]hen the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears."[7] "[B]road, conclusory statements regarding the teachings of multiple references, standing alone, are not 'evidence.'"[8])

The Applicants respectfully note that the Examiner's references individually and collectively fail to teach or suggest making the Examiner's combination. Thus, the Examiner's references fail to establish *prima facie* obviousness of the claims.

In view of the above, the Applicants respectfully request that this rejection be withdrawn.

c. There is no Reasonable Expectation of Success in the Examiner's Combination of Torroni and Aaserud

In the Office Action of January 24, 2007 the Examiner notes:

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[4] *In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990).
[5] MPEP §2143.01.
[6] *In re Ricjckaert*, 28 USPQ2d 1955 at 1956 (Fed. Cir. 1993).
[7] See *Id.* At 1957.
[8] *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614 (Fed. Cir. 1999).

"One skilled in the art would have been motivated to combine the method of analyzing mtDNA as taught by Torroni et al. with a step determining base composition measurement by using mass spectrometry as taught by Aaserud et al. because the ordinary artisan would have a reasonable expectation of success that inclusion of said limitation would result in a sensitive comparison of base composition variations in mtDNA and accurate measurement of base compositions in said target because Aaserud et al explicitly taught that the mass spectrometry measures accurate molecular masses thereby providing correct base compositions of a target nucleic acid (see abstract on page 1266) and such modification is considered as obvious over cited prior art." (Office Action of January 24, 2007, page 6). (Emphasis added.)

The Applicants respectfully disagree. Torroni does not teach or suggest the forensic methods of mitochondrial DNA analysis of the presently claimed invention. Accordingly, Torroni provides no instruction, teaching or suggestion to the ordinary artisan how to go about combining the inumerable combinations of Aaserud's methods with Torroni's haplogroups to arrive at the presently claimed invention. Alone and in combination, Torroni and Aaserud fail to teach, suggest or instruct the artisan of ordinary skill how to go about selecting and operating components (for example, forensic evidence samples, amplification primers, amplification conditions, and databases) of the forensic methods of mitochondrial DNA analysis of the present application. Torroni is silent. Aaserud is silent.

In the Office Action of January 24, 2007 the Examiner has not advanced any evidence in support of the contention that the ordinary artisan using Torroni's population haplogroups and Aaserud's methods of synthetic ssDNA analysis, would have a reasonable expectation of success in arriving at the forensic methods of mitochondrial DNA analysis of the present application. Because the Examiner is not able to show that a reasonable expectation of success may be found in Torroni plus Aaserud, the third prong of a *prima facie* case of obviousness is defective, as are prongs one and two.

In view of the above, the Applicants respectfully request that this rejection be withdrawn.

2. Torroni in View of Aaserud and further in View of Oefner

In the Office Action of January 24, 2007 the Examiner argues:

> "Torroni et al in view of Aaserud et al. teach a method of mtDNA analysis as discussed in 6A above. However neither Torroni et al. nor Aaserud et al. teach that the subjects are non-human organisms, fungi, parasites or protozoa. Oefner et al. teach a method for detecting polymorphisms in subjects using PCR-RFLP to identify genetic variability across a population and to provide polymorphism databases for the purposes of forensic identification of an individual or for linkage analysis or population studies (see col. 5 line 6-48, col. 14, line 49 – 59), where Oefner discloses that the subjects include a number of microorganisms including bacteria, parasites, and infectious agents like viruses (see col. 14. line 60 – 67 and analysis of mtDNA (see col 15, line 6-13)." (Office Action of January 24, 2007, page 7.)

The Applicants respectfully disagree. The Examiner's combination of Torroni in view of Aaserud and further in view of Oefner, fails to teach multiple elements of the presently claimed invention. The Applicants note that dependent claim 53 (formerly claim 18) and dependent claim 72 (formerly claim 38), are not obvious for at least the same reasons that base claim 46 (formerly claim 13) and base claim 65 (formerly claim 34) are not obvious. As discussed above (Section III.C.1.) the Applicants note that the Examiner's combination of Torroni and Aaserud both individually, and in combination, fail to render claims 46 and 65 obvious. Oefner's description of detection of polymorphisms by denaturing HPLC does not remedy the defects of the Examiner's combination of Torroni and Aaserud. Thus, the Examiner's references fail to establish *prima facie* obviousness of the claims.

In view of the above, the Applicants respectfully request that this rejection be withdrawn.

IV. STATUS OF THE OBJECTION TO THE DRAWINGS

In the Office Action of January 24, 2007 the Examiner notes:

> "With regard to the objection to the Drawings (Fig 20A and 20B), Applicants' arguments and amendment are fully considered and found persuasive in part. The amendment did not incorporate SEQ ID No. in the Fig 20A and 20B, which represents sequences with more than 10 bases. Thus, the objection to the drawings is maintained herein." (Office Action of January 24, 2007, page 8).

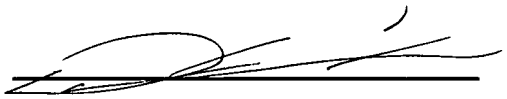
In the present Amendment and Response to the Office Action of January 24, 2007, SED ID Nos. 44 and 45 have been added to Figure 20A, and SEQ ID Nos. 46 and 47 have been added to Figure 20B. Please see the labeled Replacement Sheets that are attached to this document.

In view of the above, the Applicants respectfully request that this objection be withdrawn.

CONCLUSION

All grounds of rejection of the Office Action of January 24, 2007 have been addressed, and reconsideration of the application is respectfully requested. It is respectfully submitted that Applicant's claims as amended should be passed into allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 218-6900.

Dated: May 2, 2007



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